REMARKS

Claims 18 and 25-35 are pending. Claims 31 and 35 are rejected under 35 U.S.C. § 102, claims 18 and 25-35 are rejected under 35 U.S.C. § 103, and claims 18, 25-28, and 31-35 are rejected on the ground of nonstatutory obviousness-type double patenting. Applicants address each basis for rejection as follows.

Rejection under 35 U.S.C. § 102

Claims 31 and 35 are rejected under 35 U.S.C. § 102(b) as being anticipated by Niswender (U.S. Patent No. 4,336,185; "Niswender"). In particular, the Office states (page 2):

> Niswender (US 4,336,185) teaches of a receptor binding conjugate comprising three components, 1.) an antibody fragment, such as a tyrosine, 2.) a radionuclide or radionuclides and 3.) folic acid and salts, esters, and amides thereof and methods of making the conjugates. (Citation omitted.)

Applicants respectfully disagree.

Claim 31 is directed to a conjugate consisting of (i) a radionuclide, (ii) an antibody, antibody fragment, or antibody construct, with affinity for a tumor associated antigen, and (iii) at least one non-cytotoxic folate. Applicants submit that, as detailed below, Niswender fails to describe a conjugate meeting all the limitations of claim 31, and therefore cannot anticipate claim 31 or dependent claim 35.

Niswender does not describe a conjugate containing a radionuclide, at least one non-cytotoxic folate, *and an antibody, antibody fragment, or antibody construct.* The

Office appears to assert that a conjugate containing *tyrosine* contains an antibody fragment. Applicants submit that the terms "antibody, antibody fragment, or antibody construct" would not, by one of skill in the art, be considered to encompass a single amino acid such as tyrosine. The claims refer to an *antibody* fragment. As such, some functional or structural feature of an antibody would need to be maintained for one skilled in the art to recognize that the fragment is an *antibody* fragment. A single amino acid (e.g., tyrosine) clearly does not possess sufficient structural or functional features for the amino acid to be considered an antibody fragment.

Moreover, claim 31 requires the antibody, antibody fragment, or antibody construct to have *affinity for a tumor associated antigen*. Nowhere does Niswender teach that tyrosine has affinity for a tumor associated antigen.

In addition, with regard to Niswender, the Office states (page 2):

> The intermediate folate thyroglobulin conjugate is also disclosed albeit without the radionuclide coupled folate-antibody conjugate.

In response, Applicants note that thyroglobulin is not an antibody (or antibody fragment or antibody construct). Thyroglobulin is a massive 500+ Kd protein with no known correspondence to the structure of an antibody other than the fact that both are polypeptides. Niswender also fails to provide any indication that thyroglobulin has affinity for a tumor antigen as required by claim 31.

In sum, Niswender fails to teach each and every element of the claimed invention, namely a conjugate containing a radionuclide, at least one non-cytotoxic folate, *and an*

antibody, antibody fragment, or antibody construct with affinity for a tumor associated antigen, and therefore cannot anticipate claims 31 or 35. The present rejection under 35 U.S.C. § 102 should be withdrawn.

Rejection under 35 U.S.C. § 103

Claims 18 and 25-35 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Sinkule et al. (EP 282057; "Sinkule") in view of Wedeking (U.S. Patent No. 6,093,382; "Wedeking"), and claims 18, 25-28, and 30-35 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Niswender in view of Wedeking and Goldenberg et al. (U.S. Patent No. 5,698,178; "Goldenberg"). Applicants respectfully traverse these bases for rejection as follows.

Sinkule and Wedeking

The Office states (page 3):

> Sinkule et al. (EP 282057) discloses a receptor binding conjugate comprising three components, 1.) a monoclonal antibody, 2.) a radionuclide and 3.) a chemotherapeutic agent, such as folate or analogues thereof. (Citations omitted.)

In response, Applicants submit that Sinkule in no way teaches or suggests a conjugate including a folate. Applicants' claims recite that the folate is *non-cytotoxic*. In Sinkule, folate analogues are indeed disclosed as examples of chemotherapeutic agents, but these cannot be true folates because a chemotherapeutic is by nature cytotoxic and folates are

essential nutrients and therefore are non-cytotoxic, as recited in the claims. Applicants note that the nature of Sinkule's disclosure is evident from the title ("Chemo-Radio-Immuno-Conjugates"), as well as the abstract and the text. Clearly, the document is directed to "Chemo-radio-immuno-conjugates." In particular, Sinkule states, at the top of the second column:

> There also remains a need for improved therapeutic agents that are efficacious against cells that have developed radiation resistance but not chemotherapy resistance, and against cells that have developed chemotherapy resistance but not radiation resistance.

It is the stated need and object of Sinkule to provide cytotoxic agents having both chemotherapeutic and radiotherapeutic components. This is achieved by conjugating both a chemotherapeutic agent and a radioisotope to a targeting antibody carrier. A large number of possible chemotherapeutic agents are considered useful in Sinkule, of which folate-analogues are one class, but, crucially, all of the chemotherapeutic agents fulfill the essential requirement of having chemotherapeutic value.

In contrast to the teaching of Sinkule, the conjugates of the present claims have no chemotherapeutic effect – the folate component of the conjugate is non-cytotoxic. These conjugates include a radioisotope, but do not address the stated object of Sinkule to provide conjugates effective against cells that have developed radiation resistance.

Moreover, Applicants note that, in the administration of radioisotopes, the limiting factor in dosage is frequently the level of control which can be exerted over the fate of the radionuclide and any daughter isotopes. The present inventors have established that

conjugates having a dual-binding ability, where an antibody (or antibody fragment or construct) component targets a tumor-specific antigen and a non-cytotoxic folate targets the folate binding protein, provide highly effective delivery and control of the radionuclide. This high level of control is neither suggested nor taught by Sinkule and runs contrary to the primary teaching of Sinkule that dual cytotoxic agents are of value.

The Office cites Wedeking as teaching the use of folate as a targeting method. Wedeking, however, does not indicate any advantage in the use of a dual-targeting conjugate with two separate tumor-binding components. Furthermore, Wedeking does not provide any teaching or suggestion to a skilled worker in addressing the object of Sinkule in providing dual cytotoxic effect; namely why one skilled in the art would substitute a non-cytotoxic folate for a cytotoxic chemotherapeutic in a conjugate.

In sum, Sinkule provides a conjugate that contains two cytotoxic components, a radionuclide and a chemotherapeutic, and states that the object of the invention is to provide therapeutic agents that are efficacious against cells that have developed radiation resistance but not chemotherapy resistance, and against cells that have developed chemotherapy resistance but not radiation resistance. As such, both cytotoxic components, the radionuclide and the chemotherapeutic, are essential to meet the object of Sinkule's invention. There simply is no teaching or suggestion to replace the cytotoxic chemotherapeutic agent with a non-cytotoxic folate. The fact that Wedeking describes using folate as a targeting method does not remedy this deficiency in Sinkule's teaching.

To substitute non-cytotoxic folate for the chemotherapeutic agent is simply contrary to the teaching of Sinkule. The fact that some of the possible chemotherapeutic agents disclosed in Sinkule are folate analogues makes no difference to the desirability of making this substitution. Substituting a non-cytotoxic compound for a cytotoxic compound completely alters the nature of Sinkule's conjugate. Applicants submit that the Office has failed to show that one skilled in the art would have been motivated to combine the cited references as indicated. This basis of the 35 U.S.C. § 103 rejection should be withdrawn.

Niswender, Wedeking, and Goldenberg

In rejecting claims 18, 25-28, and 30-35 over Niswender in view of Goldenberg and Wedeking, the Office states (page 7):

> At the time of the invention it would have been obvious to one ordinarily skilled in the art to ... utilize an antibody (fragment)-folate-radionuclide conjugate for the method of targeting a radionuclide to a malignant cell as Goldenberg et al. discloses targeting the antibody-radionuclide or antibody-folic acid analog to tumor cells and Wedeking et al. specifically discloses the targeting of gadolinium-folate (folic acid) conjugates to ovarian cancer cells.

The Office's rejection is also based on the asserted disclosure, in Niswender, of a conjugate including tyrosine or thyroglobulin and, therefore, including an antibody or antibody fragment. As discussed above, neither tyrosine nor thyroglobulin is an antibody or antibody fragment and neither of these shows the required binding affinity for a tumor

associated antigen. Also, as discussed below, Niswender does not relate to therapeutics and thus is not likely to be combined with one of the other citations to provide such agents. Furthermore, Niswender, Wedeking, and Goldenberg fail to address the dual binding conjugate recited in the claims. The conjugates encompassed by the present claims, in addition to a radionuclide, contain two binding components, (i) an antibody, antibody fragment, or antibody complex with affinity for a tumor associated antigen and (ii) a non-cytotoxic folate. This concept is neither taught nor suggested by the cited references alone or in combination.

Goldenberg describes conjugates containing folic acid analogs, however, these folic acid analogs, like those of Sinkule, are described as chemotherapeutic agents (see, e.g., column 23, lines 55-60). Chemotherapeutic agents are toxins that kill cells. Clearly any folic acid analogs described by Goldenberg are not *non-cytotoxic folates*. Moreover, Goldenberg fails to make any suggestion to generate a conjugate containing a non-cytotoxic folate or that there would be any benefit in doing so.

Wedeking, as noted above, describes using folate as a targeting method. Wedeking provides no teaching or suggestion to use a conjugate containing a non-cytotoxic folate *and* an antibody or antibody fragment to target a tumor associated antigen. Applicants submit that the Office has failed to establish that one skilled in the art would be motivated to combine the references as suggested by the Office to arrive at the presently claimed invention. This basis of the 35 U.S.C. § 103 rejection should also be

withdrawn.

With regard to Niswender, Applicants also note that this reference relates to a "radioimmunoassay of body fluids to determine folate." This is an *in vitro* test, and the compositions disclosed in Niswender relate to this assay. Niswender teaches that folic acid may be derivatized (conjugated) to a protein or to radioactive iodine. The radioactive folate conjugates are for use in an *in vitro* assay, where they compete against folate from a body fluid sample for binding to folate binding protein or to an antibody raised by using the folate-protein conjugate (see Example 6).

Niswender states that the products of the invention are useful in the determination of folic acid, i.e., they can be used in an *in vitro* assay or analytical method. There is absolutely no disclosure in Niswender of folic acid conjugates for a therapeutic purpose. Niswender does not teach the use of conjugates of folic acid as therapeutic agents and so cannot teach towards the use of such against cancerous cells and tissues expressing folic acid binding protein. Niswender solely elaborates on how folic acid conjugates can be used in an assay of folic acid. One use is as a competitive binder and a second use is to induce antibodies for use in the assay method.

There is also no disclosure in Niswender of administering any radioisotope to a body, much less administering an antibody or antibody fragment or construct to a body. None of the proteins exemplified in Example 1 of Niswender (columns 4-5) are antibodies, but rather blood serum proteins, chosen to be large and likely to stimulate an

immune response. The only antibodies referred to in Niswender are those generated in the blood stream of a vertebrate as a result of administering a protein-folate conjugate (see passage bridging columns 1 and 2). Niswender does not teach or suggest conjugation of folic acid to an antibody, thereby producing a molecule having dual binding properties, or that a radionuclide can be attached to the antibody in any way.

As indicated above, Niswender does not disclose conjugates having both a protein component and a radioisotope. Niswender simply discloses two different conjugates having two distinct uses.

Nonstatutory obviousness-type double patenting

Claims 18, 25-28, and 31-35 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 6,740,304 ("the '304 patent"). The Office states (page 8):

> Although the conflicting claims are not identical, they are not patentably distinct from each other because the method of delivering therapeutic radiation to a patient with a malignant cell of US 6,740,304B2 encompasses the method of targeting a radionuclide to a malignant cell within a subject of the instant claims.

Applicants respectfully disagree.

Claims 1-6 of the '304 patent recite conjugates including a folate, a radionuclide or mixture of radionuclides, and an *inert* human IgG or IgM antibody or antibodies or a fragment or construct thereof. The inert human IgG or IgM antibody has considerable

advantages as a carrier in providing advantageous circulation times, but does not provide any targeting effect.

In contrast to the above, the antibody (or antibody fragment or antibody construct) component of the conjugates of the present invention provides a targeting effect. The claims require the antibody, antibody fragment, or antibody construct to have *affinity for a tumor associated antigen*. Given that the antibodies recited in claims 1-6 of the '304 patent are *inert*, these claims do not teach or suggest using antibodies, antibody fragments, or antibody constructs in a conjugate where the antibody component has *affinity for a tumor associated antigen*. Applicants submit that the nonstatutory obviousness-type double patenting rejection over claims 1-6 of the '304 patent should be withdrawn.

CONCLUSION

Applicants submit that the application is now in condition for allowance, and this action is hereby respectfully requested.

Enclosed is a Petition to extend the period for replying to the final Office Action for three (3) months, to and including September 7, 2007, and a check in payment of the required extension fee.

If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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